population are 18.5% for males and 9.8% for females. **CONCLUSIONS:** Random sampling from patient level data provided the best approximation of actual NHANES population predicted CVD rates. The cholesky decomposition approach was slightly limited since only continuous variables could be utilized which could explain the deviation from the population predicted CVD rates. Independent sampling underestimated the mean risk by ~20%, an interesting finding as many individual simulation models created patients with this approach. Researchers should be cautious in their use of summary statistics when populating individual simulation models.

PRM74

VALIDATION OF THE SPHR DIABETES PREVENTION MODEL

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OBJECTIVES: We have developed a model to evaluate type-2 diabetes prevention interventions. We aimed to validate this model against external data to test the accuracy of model predictions. **Methods**An individual patient simulation was developed to predict longitudinal trajectories of HbA1c, 2-hr glucose, FPG, BMI, systolic blood pressure, total cholesterol and HDL cholesterol based on statistical analyses of the Whitehall II longitudinal cohort. Criteria for diabetes diagnosis were flexibly specified. Cardiovascular events were estimated from the QRISK2 algorithm. Microvascular complications of diabetes were estimated from the UKPDS outcomes model. Several validations were performed to compare model outcomes with reported data from external sources. We assessed the predicted diabetes incidence using data from the EPIC Norfolk cohort. Data from the Health Survey for England (HSE) 2003 cohort was simulated for eight years to compare predicted disease incidence and metabolic distributions with HSE 2011 data. We compared microvascular, cardiovascular and mortality outcomes in a diabetic population with those observed in the UKPDS. We assessed the performance of the model in predicting the results of the ADDITION trial for diabetes screening. **RESULTS:** We found that the model overestimated three-year incidence of diabetes, particularly in high risk (HbA1c>6.0) individuals, but underestimated diabetes incidence in medium risk individuals (HbA1c 5.5-5.9) compared with the EPIC-Norfolk data. Predictions from HSE 2003 were fairly accurate. Predictions for microvascular events were similar to the UKPDS, but cardiovascular disease and mortality were slightly under-predicted. The model replicated the non-significant difference seen between control and intervention arms of the ADDITION trial, but overestimated total mortality and cardiovascular disease. **CONCLUSIONS:** The SPHR Diabetes model appears to be fairly accurate at predicting external data, but has a tendency to overestimate mortality rates in a newly diagnosed diabetic cohort, and underestimate cardiovascular disease and mortality compared with the UKPDS.

PRM75

USE OF MODEL AVERAGING TECHNIQUES IN COST-EFFECTIVENESS ANALYSIS IN ONCOLOGY

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OBJECTIVES: Often in cost-effectiveness analysis (CEA) of oncologic drugs, survival data from a randomized controlled trial are extrapolated to a lifetime horizon using parametric regression techniques. To capture parameter uncertainty in the analysis, regression parameters along with other model parameters are varied in probabilistic sensitivity analysis. However, structural uncertainty in the choice of regression model is rarely investigated. This study discusses the use of model averaging and provides an example to address structural uncertainty in CEA. **METHODS:** Using a cohort partition model, the numbers of patients in "progression-free", "progressed", and "dead" health states were calculated directly from progression-free survival (PFS) and overall survival (OS) curves. Weibull, exponential, lognormal, log-logistic, generalized gamma, and Gompertz parametric models were used to extrapolated these curves to a lifetime horizon. Total costs, life year (LY), and quality adjusted life year (QALY) for each regression model were estimated. Weighted results across all models were calculated, based on weights that were derived from Akaike's or Bayesian Information Criterion (AIC or BIC) parameters. **RESULTS:** Evaluating solely on BIC values, the lognormal distribution was identified as the best model for both survival curves. This resulted in the lowest observed ICERs. When model selection was based on considerations involving the log-cumulative hazard plots, clinical plausibility, and AIC/ BIC for each distribution, the Weibull distribution was selected for both curves, resulting in a 29% and 27% increase in the ICER for QALY and LY, respectively. Similar increases were observed when model averaging was applied using BIC-derived weights. In this case, model averaging produced results that were similar to those where model selection was based on multiple criteria. **CONCLUSIONS:** Choice of parametric models often has the biggest impact on the outcomes in CEAs in oncology. Model averaging takes into account the structural uncertainty surrounding the choice of parametric models.

PRM76

COMPARING THREE DIFFERENT METHODS OF HALF-CYCLE CORRECTION

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OBJECTIVES: To compare three different half-cycle correction methods and their effect on the final results of Markov models. **METHODS:** To assess the relative performance of the alternatives to the standard half-cycle correction we constructed a 5-state Markov model where the courses of the number of patients in health states follow different shapes to represent the most likely cases in modelling practise. We applied three different correction methods (standard half-cycle correction, Simpson's method and using the mid-cycle values) and we also looked at the results without any correction and with different numbers of Markov cycles. We conducted a sensitivity analysis by changing the input parameters of our model. In total we examined 80 cases. **RESULTS:** In our Markov model Simpson's method provided the most accurate results where the difference from real data was less than 0.1% in 67 of the 80 cases. The second most accurate method was using the mid-cycle values. The standard half-cycle correction method provided more accurate results than calculations without any kind of half-cycle correction with the exception of one set of input parameters. **CONCLUSIONS:** Based on our model the most accurate method for half-cycle correction is Simpson's method as in most cases it was the closest to real data. It is important to note that with a few exceptions even the standard method's results were more accurate than in cases where no half-cycle correction was applied.

PRM77

APPLICATION OF A MODEL OF DECISION BASED ON FUZZY LOGIC TO PHARMACOECONOMICS: TREATMENT OF CROHN'S DISEASE WITH ANTITNF IN OUT OF LABEL USE

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OBJECTIVES: We present a model decision based on fuzzy logic, and apply to off label use of antiTNF in Crohn's disease (CD) (Infliximab (IFB) 10 mg/kg/8 weeks, adalimumab (ADA) 80mg/2 weeks,. Certolizumab (CZB) 200mg/2weeks). The term "fuzzy logic" (FL) was introduced in 1965 by LAZadeh. Compared to traditional logic, FL variables may have a truth value in degree. FL has been applied to many fields, from economic analysis, to artificial intelligence. However it has not been applied so far to pharmacoeconomics. **METHODS:** According to a decision analysis model based on FL four fuzzy variables that affect the choice of treatment are defined: treatment success (expressed as a probability), cost of success, cost of failure (expressed as inverses), and other conditions about the cost (negotiation, handling of drugs...). Based on the value of these fuzzy variables, three linguistic variables (High, Medium, Low) are defined to expressing convenience of choice. The combination of the three possible values for each of the variables gives us 81 possible decision rules, so that the (HHHH) would be the most favorable option and (LLLL) the more unfavorable. So a new fuzzy variable called "ranking" is established for classifying these options with 7 possible values (Very-unfavorable, unfavorable, slightly-unfavorable, neutral, slightly-favorable, favorable, very-favorable). The value of the fuzzy variables for antiTNF at 52 weeks of treatment, were established based recent meta-analysis and reviews. **RESULTS:** The matrices obtained and corresponding decision rules were: for IFB (0.65, 6.3 10-5, -1.17 10-4, 0.075) / (MMML); For ADA (0.41, 9.21 10-5, 6.4 10-5, 0.075) / (MMML); for CZB (0.52, 1.30 10-4 1.5 10-4 0.075) / (MHHB). Thus the CZB would be the "slightly-favorable" option, versus IFB and ADA (unfavorables). **CONCLUSIONS:** It possible to apply methods of "FL" to pharmacoeconomic studies According to the model, Certolizumab would be a most favorable choice in off-label use for CD.

PRM78

MULTI-CRITERIA DECISION ANALYSIS (MCDA): TESTING A PROPOSED MCDA MODEL FOR ORPHAN DRUGS

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OBJECTIVES: Since the introduction of the orphan drugs in Europe, it has been suggested that the general method of appraising drugs for reimbursement is not necessarily suitable for orphan drugs. The National Institute for Health and Clinical Excellence indicated that several criteria other than cost and efficacy could be considered in reimbursement decisions for orphan drugs. The aim of this study was to apply a MCDA framework that was proposed by Hughes-Wilson *et al* (2012) to a range of orphan drugs in different diseases to test the correlation between drug price and aggregated MCDA scores for each product. **METHODS:** A MCDA framework was developed using the nine criteria suggested by Hughes-Wilson *et al*. A supplementary literature review was conducted to identify other attributes described in the application of MCDA in rare diseases. A numerical scoring system on a scale of one to three was developed for each criterion. Correlations between the average annual cost of the drugs and aggregate MCDA scores were tested and plotted graphically. Different weightings for each of the attributes were also tested. A further analysis was conducted to test the impact of including the drug cost as an attribute in the aggregate index scores. **RESULTS:** The literature review identified further commonly cited criteria: 'convenience of administration', 'age of the target population', 'quality of life', and 'drug innovation' that were added to the aggregate index scores. In the drugs studied, the $R^2$was 0.808 and 0.704 when costs were included and not included, respectively. The standard error of the slope varied from 7711.9 to 11413.3 when costs were included and not included, respectively. **CONCLUSIONS:** This quantitative study provided insight into using MCDA and its relationship to annual costs. Further work should explore the potential for therapy-specific MCDAs and how to inform value-based pricing assessment.

PRM79

ADVISHE: A NEW TOOL TO REPORT VALIDATION OF HEALTH-ECONOMIC DECISION MODELS

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BACKGROUND: Modelers and reimbursement decision makers could both profit from a more systematic reporting of the efforts to validate health-economic (HE) models. **OBJECTIVES:** Development of a tool to systematically report validation efforts of HE decision models and their outcomes. **METHODS:** A gross list of model validation techniques was collected using a literature review, including sources outside the HE field. A panel then selected the most important items. Based on the Delphi method, the panel members could score items in three e-mail rounds. Participants were HE modelling experts, covering various nationalities and work environments. They could comment on relevance, feasibility and formulation of the items and received feedback on comments from others. This resulted in a draft tool of selected items, which was tested and improved in two further rounds. In

addition, the Dutch National Health Care Institute commented on usefulness for decision makers, while a separate group of 50 HE experts could comment during a workshop at ISPOR Montreal 2014. **RESULTS:** 35 Validation techniques were identified and grouped into four categories: conceptual model validation, computerized model validation, data validation and operational validation. Around 30 HE experts commented in each of the first three Delphi rounds, resulting in a 15 item draft tool. The Dutch health care advisory institute suggested to add one more item. Participants from the ISPOR workshop delivered 19 filled-in questionnaires. A fourth round resulted in 17 responses. This led to a refined version containing 16 items, which is currently sent out for a final, fifth round. **CONCLUSIONS:** When filled out by the modellers, AdVISHE (Assessment of the ValIdation Status of Health-Economic decision models) supports model users in assessing the validation status of a model It will be useful as part of reimbursement dossiers, by providing systematic and transparent insight into the validation efforts performed and their results.

PRM80

MODELLING SURVIVAL IN THE PRESENCE OF DIFFERENT MECHANISMS OF ACTION: IPILIMUMAB AND VEMURAFENIB IN ADVANCED MELANOMA

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OBJECTIVES: Traditional indirect treatment comparison methods assume the underlying survival profiles of treatments are similar (i.e. proportional hazards). This assumption is unlikely to hold for the comparison of ipilimumab and vemurafenib: Whereas vemurafenib exhibits improved short-term survival compared with ipilimumab, pooled study data for ipilimumab consistently show that patients achieve durable long-term survival. We present a method to compare across trials with differing survival profiles by accounting for follow-on treatments and different patient baseline characteristics. **METHODS:** Comparative survival estimates for ipilimumab and vemurafenib were produced using patient-level data from trial CA184-024 for ipilimumab and published survival curve fits from BRIM-3 (along with registry data) for vemurafenib. The BRIM-3 vemurafenib overall survival curve was adjusted to account for (a) the effect of second-line ipilimumab (via a tunnel-state methodology) and (b) differences in patient baseline characteristics between BRIM-3 and CA184-024, by means of a model (Korn model), constructed to predict the outcomes for dacarbazine-treated patients. The resulting survival estimates were compared with naïve unadjusted survival curve fits, and estimates produced using a hazard ratio (from an indirect comparison) to the ipilimumab data. **RESULTS:** Estimated survival for ipilimumab was 3.3 years (mean). Predicted survival for vemurafenib, using a naïve comparison, was 3.0 years (mean). Adjusting for second-line ipilimumab and different baseline characteristics resulted in an estimate of 2.8 years for vemurafenib. When a hazard ratio was applied to the ipilimumab data, which underlies the here strong assumption that the vemurafenib overall survival profile is similar to that of ipilimumab, predicted survival for vemurafenib increased to 4.2 years.**CONCLUSIONS:** Depending on the methodology used, the mean predicted survival for vemurafenib varied from 2.8 to 4.2 years. Alternative methods that incorporate the long-term survival profile of ipilimumab (naïve comparison or more sophisticated adjustment methodology) demonstrate a higher number of life years with ipilimumab versus vemurafenib.

PRM81

HEALTH ECONOMIC MODELS IN ALZHEIMER'S DISEASE: A CRITICAL ASSESSMENT

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OBJECTIVES: Alzheimer's Disease destroys brain cells, causing problems with memory, thinking, and behavior severe enough to affect work, family and social relationships, and, eventually, the most basic activities of daily living. Different treatment options have been introduced and evaluated from a health economic perspective. However, given the specific characteristics of the disease an evaluation of existing models is needed. **METHODS:** The following databases were searched systematically: PubMed, Health Technology Assessment Database, NHS Economic Evaluation Database, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, DAHTA-database, PSYNDEX and PsycINFO. For the abstracts that met the pre-defined inclusion criteria, full text articles were obtained and evaluated for inclusion in the assessment. **RESULTS:** After eliminating duplicates the search indicated yielded 1'219 articles of which another 940 were excluded based on the title selection. Finally 59 articles have been reviewed in full text after abstract review. Out of those articles 39 were deemed to be relevant based on the research question. The majority of models (48%) have been Markov models, other methods being used were various statistical analysis applications, micro-simulation, and discrete-event simulations. Limitations of existing models include the following: Focus on cognitive function as disease progression only; lack of inclusion of correlation between disease progression and other factors (e.g. residential status); lack of complete structure of diagnosis and treatment of disease (e.g. including non-drug treatments). Based on the Drummond checklist for health economic models the quality of models proved generally to be high but the majority of those lack presenting a comprehensive pathway of the natural history of the disease. **CONCLUSIONS:** Current models do not allow decision makers optimally characterizing the disease, to better assess the costs and benefits of a wide range of potential interventions. Potential new models need to take the disease characteristics and specifics more appropriate into account.

PRM82

APPROACHES USED TO MODEL THE RELATIONSHIP BETWEEN PROGRESSION-FREE SURVIVAL (PFS) / TIME-TO-PROGRESSION (TTP) AND OVERALL SURVIVAL (OS) WITHIN HEALTH ECONOMIC MODELS OF CANCER THERAPIES

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OBJECTIVES: Within health economic models of metastatic cancer therapies assumptions on the relationship between progression-free survival (PFS) / time-to-progression (TTP) and overall survival (OS) are typically required; notably when OS data are immature or unavailable. A review was undertaken to identify the methods that have been used within health economic models regarding this relationship and to identify the rationale given for the approach taken, specifically in those situations where OS data were not available or immature. **METHODS:** All NICE technology appraisals in the advanced and/or metastatic cancer setting completed by December 2013 were reviewed. The review included all relevant appraisal documents publicly available on the NICE website containing information on the methods used and/or rationale for the approach taken to model the relationship between OS and PFS/TPP within the health economic model. This included the sponsor submission and updated analyses, the independent Assessment Report, and other reports/analyses in relation to the appraisal process. **RESULTS:** In those instances where OS data were immature or not available, PFS/TTP was typically assumed to be a valid surrogate of OS. Justification for this assumption was inconsistently reported. In some health economic models a quantification of the assumed relationship was informed by published evidence and/or expert judgement. In some cases attempts were made to explore the potential impact of this relationship in sensitivity analysis. **CONCLUSIONS:** The methods and/or rationale given for the approach used to model the relationship between OS and PFS/TTP in health economic models has been inconsistently reported and justified. Whilst some health economic models attempted to quantify this relationship, further transparency is required. A consensus needs to emerge on the most appropriate approaches to be used within health economic models to quantify this relationship, specifically when OS data are not available or immature and to identify the circumstances when particular approaches may be most relevant.

PRM83

COMPARISON OF METHODS TO ESTIMATE HEALTH STATE UTILITIES IN METASTATIC BREAST CANCER (MBC)

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OBJECTIVES: Patient-level utility values for different stages of MBC and toxicities commonly associated with chemotherapy regimens are useful for health economic assessments. Three methods to estimate utilities exist when direct utility data are not available: utility 'mapping' from existing disease-specific scales, vignette studies that describe the health states; or derivation of preference-based measures from an existing condition-specific scale. This study compares utility estimates in MBC utilizing the above methods. **METHODS:** Based on data from a phase 3 clinical trial in MBC (N=1102) utility mapping was conducted using a published regression algorithm to convert the EORTC QLQ-C30 questionnaire to the EQ-5D utility. Mean utility values were estimated for relevant health states: stable disease (SD), tumor response (TR), disease progression (DP) and common toxicities. Results were compared to previously published values obtained for a vignette study conducted in one hundred members of the general public. **RESULTS:** Observed MBC utilities were similar in mapping vs. vignette studies for SD: 0.697 vs. 0.715, and TR: 0.782 vs. 0.790. General public respondents in the vignette study assigned much lower utility to symptomatic DP (0.443) vs. imaging-based DP in mapping study (0.679); and disutility for toxicities: vomiting: 0.103 vs. 0.050; fatigue 0.115 vs. 0.029; febrile neutropenia 0.150 vs. 0.012 (vignette vs. mapping respectively). Hand-foot syndrome, stomatitis and hair loss were not associated with disutility in the mapping study (potentially due to small sample size) while disutility of 0.116; 0.151; and 0.114 were reported by the vignette study. **CONCLUSIONS:** Utilization of different methods to estimate utilities in MBC may lead to a wide range of estimated values with potentially significant implications for health economic evaluation. Caution must be exercised when comparing utility values derived using different methods. It is preferable to collect such data from patients directly and use vignettes as a last resort.

PRM84

COST-EFFECTIVENESS MODELS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): CROSS-MODEL COMPARISON OF HYPOTHETICAL TREATMENT SCENARIOS

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OBJECTIVES: To compare different COPD cost-effectiveness models with respect to structure and input parameters and to cross validate the models by running the same hypothetical treatment scenarios. **METHODS:** COPD modeling groups simulated four hypothetical interventions with their model and compared the results with a reference scenario of no intervention. The four interventions modeled assumed: 1) 20% reduction in decline in lung function, 2) 25% reduction in exacerbation frequency, 3) 10% reduction in all-cause mortality and 4) all these effects combined. The interventions were simulated for a five-year and lifetime horizon with standardization, if possible, for sex, age, COPD severity, smoking status, exacerbation frequencies, mortality due to other causes, utilities, costs and discount rates. Furthermore, uncertainty around the outcomes of intervention four was compared. **RESULTS:** Seven out of nine contacted COPD modeling groups agreed to participate. Differences in 5-year QALY gains ranged from 0.00020 to 0.039 for intervention one, 0.0089 to 0.075 for intervention two and 0.017 to 0.048 for intervention three. The difference in costs ranged from €561 to €912 for intervention one, €739 to €1350 for intervention two and €1140 to €1618 for intervention three. The 5-year cost-effectiveness ratios (ICERs) for the most comprehensive intervention, intervention four, was €17,000/QALY for two models, €25,000-€28,000/QALY for three models